

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2004/011366

International filing date (day/month/year)
06.10.2004

Priority date (day/month/year)
08.10.2003

International Patent Classification (IPC) or both national classification and IPC
C07D207/337, C07D231/12, C07D241/12, C07D307/46, C07D213/55, C07D213/56, C07D401/04, A61K31/341,

Applicant
GLAXO GROUP LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/011366

10720 07 APR 2006

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☐ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
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Box No. II Priority

1. ☒ The following document has not been furnished:

☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☐ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

**WRITTEN OPINION OF THE
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-14 (part)

because:

☒ the said international application, or the said claims Nos. 9-11 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-14 (part) are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☒ the claims, or said claims Nos. 1-14(part) are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See separate sheet for further details

**WRITTEN OPINION OF THE
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International application No.
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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	5
	No: Claims	1-4, 6-14
Inventive step (IS)	Yes: Claims	
	No: Claims	1-14
Industrial applicability (IA)	Yes: Claims	1-8, 12-14
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search has been restricted to the compounds possessing a group D as defined in claim 2, a group A as defined in claim 3 and a group R¹ starting with a carbonyl or a sulfonyl group or being an heterocyclic ring. The expression "derivatives thereof" in the claims lacks clarity and conciseness since any chemical compound can be considered as a derivative of another compound after a variable number of synthetic modification steps.

The present opinion has consequently been limited to the compounds of formula (I) wherein the group D is as defined in claim 2, the group A is as defined in claim 3 and the group R¹ is starting with a carbonyl or a sulfonyl group or being an heterocyclic ring and their pharmaceutical salts.

Claims 9-11 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1) Reference is made to the following documents :

- D1: US-B1-6 492 411 (TALLEY JOHN J ET AL) 10 December 2002 (2002-12-10)
D2: EP-A-0 647 629 (SANOFI) 12 April 1995 (1995-04-12)
D3: US-A-5 723 483 (LABEEUW ET AL) 3 March 1998 (1998-03-03)
D4: WO 01/19814 A2 (MERCK FROSST CANADA & CO; LACOMBE, PATRICK;
LABELLE, MARC; RUEL, REJEA) 22 March 2001 (2001-03-22)

- D5: EP-A-1 270 559 (J. URIACH & CIA. S.A) 2 January 2003 (2003-01-02)
- D6: EP-A-0 752 421 (ZENECA LIMITED) 8 January 1997 (1997-01-08)
- D7: M ABDUR RAHIM, P N PRAVEEN RAO AND EDWARD E KNAUS: "Isomeric acetoxo analogues of Rofecoxib: a novel class of highly potent and selective cyclooxygenase-2 inhibitors"" BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, vol. 12, 2002, pages 2753-2756, XP002315466
- D8: DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; PATHAN, M. D. ET AL: "2-Aryl-3-(2'-p-chlorophenyl-1',3',4'-oxadiazol-5'-ylphenyl)-4- thiazolidinones" XP002315470 retrieved from STN Database accession no. 2001:514183
- D9: G S TRIVEDI, N C DESAI: "Synthesis and antimicrobial activity of some 4-thiazolidinones" INDIAN JOURNAL OF CHEMISTRY, vol. 31B, 1992, pages 366-369, XP009043257
- D10: GUNTER KARIG, JAMES A SPENCER AND TIMOTHY GALLAGHER: "Direct deprotonation-transmetalation as a route to substituted pyridines" ORGANIC LETTERS, 2001, pages 835-838, XP002315468
- D11: SAUL H ROSENBERG AND HENRY RAPOPORT: "Convergent and efficient synthesis of spiro[benzofuran-3(2H),4'-piperidines]" J. ORG. CHEM., 1984, pages 56-62, XP002315467
- D12: ANNE-SOPHIE REBSTOCK, FLORENCE MONGIN, FRANÇOIS TRECOURT AND GUY QUEGUINER: "Synthesis and deprotonation of 2-(pyridyl)phenols and 2-(pyridyl)anilines" ORG. BIOMOL. CHEM., vol. 1, 18 July 2003 (2003-07-18), pages 3064-3068, XP002315469

2) Novelty (Art. 33 (1) and (2) PCT) :

Except for claim 5 relating to specific products, the present application does not comply with the requirements of Art. 33(2) PCT since numerous compounds falling in the scope of claims 1-4 are known in the pharmaceutical fields (see search report e.g. compounds of table 3 of D3).

3) Inventive Step (Art. 33 (1) and (3) PCT) :

The technical problem underlying the present application is the provision of compounds useful for the treatment of pain, inflammatory, immunological, bone, neurodegenerative or renal disorders through their affinity to EP1 receptor.

Numerous compounds are known in the art possessing a similar structure and useful for the treatment of the same type of diseases. D1 and D7 for instance disclose novelty destroying compounds useful for the treatment of inflammation and D4 to D6 disclose compounds excluded by the proviso of claim 1 but having the same activity as that presently claimed through the same mechanism of action. In view of the very close prior art, no novel unifying feature can be identified for the novel compounds claimed.

Moreover the broad terms such as "heterocyclyl", "optionally substituted" and "derivatives thereof" defining the compounds of claim 1 embrace a wide variety of groups including pharmacophores which could compete and change the activity of a compound according to the present invention possessing two pharmacophoric groups. Thus, it can not be demonstrated even in the presence of a great number of experimented results that in fact all possible variants covered by these terms would lead to compounds with the desired activity.

The present application does not comply with Art. 33(3) PCT.

4) Industrial applicability (Art. 33(1) and (4) PCT) :

For the assessment of the present claims 9-11 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

- D13: WO 03/101959 A1 (GLAXO GROUP LIMITED; GIBLIN, GERARD, MARTIN, PAUL; HALL, ADRIAN; HEALY) 11 December 2003 (2003-12-11)
D14: WO 2004/083185 A2 (GLAXO GROUP LIMITED; GIBLIN, GERARD, MARTIN,

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International application No.

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PAUL; HALL, ADRIAN; LEWEL) 30 September 2004 (2004-09-30)